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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,055	GERDAY ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1 and 2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6 and 9-22* is/are rejected.

7)☒ Claim(s) *7 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's preliminary amendment of the drawings in the paper of 5/10/2005, is acknowledged. Claims 1-22 are still at issue and are present for examination. Applicant's comments regarding the claims in the paper of 3/18/2004, pages 3-5, are acknowledged, however, found somewhat confusing, as it is unclear if applicants are referencing the instant application or the issued parent application, 09/510,136.

Election/Restrictions

Applicant's election with traverse of Group III, Claims 3-22, in the paper of 10/2/2006, is acknowledged. The traversal is on the ground(s) that the examiner has not even alleged that an undue burden would be required in examining the full scope of the claims.

Applicant's argument is not found persuasive because as previously stated, the inventions are distinct for the reasons previously stated and the search for the different groups, I through III, are not coextensive. It is this basis of additional burden of expanding the search with the additional groups that would lead to an undue burden in the examination of additional groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1 and 2 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statement, filed 3/18/2004, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities: On page 3, lines 25-29 the specification refers to the cold-active beta-galactosidase as having a stable enzymatic activity at temperatures up to below 8°C, preferably up to below 6°C, and specifically at 4°C..." Specifically, applicants recitation of "up to below" is confusing when describing the conditions at which the claimed beta-galactosidase has stable enzymatic activity. It is believed that the claimed enzyme has stable enzymatic activity above 8°C, and that a limitation of applicants claimed beta-galactosidase is that this enzymatic activity is maintained as the temperature moves down to below 8°C, not up to below 8°C. Further, the abstract has a similar recitation as discussed above.

Appropriate correction is required.

Claim Objections

Claims 7 and 8 are objected to because of the following informalities:

Claims 7 and 8 depend from rejected claim 3.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5, and 9-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3-5, and 9-22 are directed to all possible DNAs encoding cold-active beta-galactosidase enzymes, specific for lactose, having a stable enzymatic activity up to below 8°C and plasmids and cells comprising said DNA. The specification, however, only provides a single representative species isolated from *Pseudoaltermonas haloplanktis*, having the sequence of SEQ ID NO: 1, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties other than the activities recited in the claims, for which no predictability of structure is apparent. Further, applicants have only defined a single psychrophilic bacterium, *Pseudoaltermonas haloplanktis* as a source of the claimed DNA, while

applicants claim said DNAs from at least all psychrophilic bacterium. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 3-5, and 9-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA encoding a cold-active beta galactosidase isolated from a psychrophilic bacterium, having the sequence of SEQ ID NO: 1, does not reasonably provide enablement for any DNA encoding any cold-active beta galactosidase having a stable enzymatic activity at a temperature below 8°C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 3-5, and 9-22 are so broad as to encompass any DNA encoding any cold-active beta-galactosidase enzyme, specific for lactose, having a stable enzymatic activity below 8°C. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA encoding enzymes broadly encompassed by the claims, including all DNAs encoding any cold-active beta-galactosidase enzymes and variants thereof. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed enzymes. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that cold-active beta galactosidase isolated by the psychrophilic bacterium *Pseudoaltermonas* haloplanktis having the amino acid sequence of SEQ ID NO: 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the

desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA encoding any cold-active beta galactosidase because the specification does not establish: (A) regions of the protein structure which may be modified without effecting beta-galactosidase activity; (B) the general tolerance of cold-active beta-galactosidases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a cold-active beta-galactosidase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the cold-active beta-galactosidase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those DNAs encoding polypeptides of the claimed genus having the claimed beta-galactosidase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any cold active beta-galactosidase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those DNAs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claim 6 appears to employ a novel strain of an isolated psychrophilic bacterium. Since the psychrophilic bacterium, *Pseudoaltermonas haloplanktis* is essential to the claimed cold-active beta-galactosidase, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The organism is not fully disclosed, nor has it been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the psychrophilic bacterium, *Pseudoaltermonas haloplanktis*.

It is noted that applicants have deposited the organism under the Budapest treaty at the Belgian Coordinated Collections of Microorganisms (BCCM™), but there is no indication in the specification as to public availability. As the deposit was made under the terms of the Budapest Treaty, an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-5, 9-22 are rejected under 35 U.S.C. 102(a) as being anticipated by Francois et al. (Database EMBL on line, Accession No. AJ131635, December 1998, See IDS).

Francois et al. teach a DNA comprising a sequence which encodes a cold-adapted bacterial β-galactosidase isolated from psychrophilic bacterium TAE 79. Francois et al. further teach the above DNA in a recombinant plasmid comprising an expression control sequence and bacterial cells transformed with said plasmids. The

DNA taught by Francois et al. further hybridizes to a DNA that encodes a cold active b-galactosidase specific for lactose and having stable enzymatic activity below 8oC and is produced by *Pseudoaltermononas haloplanktis*.

While Francois et al. do not teach that the β-galactosidase isolated from psychrophilic bacterium TAE 79 has each of the claimed characteristics (i.e. specificity for lactose and stable enzymatic activity at a temperature below 8°C), these are considered an inherent property of the β-galactosidase isolated from psychrophilic bacterium TAE 79, taught by Francois et al. based on the reference of Hoyoux et al. (Applied and Environmental Microbiology, Vol 67, No. 4, pages 1529-1535, April 2001, Ref: V, Form-892).

Although not considered to be prior art, Hoyoux et al. is from the same group as Francois et al. as both of the authors of Francois and Hoyoux are also authors of the later Hoyoux et al. reference. Hoyoux et al. teach the purification of the β-galactosidase from *Pseudoaltermonas haloplanktis* TAE 79 and teach that the EMBL accession number of the sequence reported is AJ131635, the same accession number as Francois et al. above. Therefore, the protein of Hoyoux et al. is the same as the protein of Francois et al. Further, Hoyoux et al. teach that the disclosed bacterium *P. haloplanktis* TAE 79 was isolated from seawater on necrosed algae at the J.S. Dumont d'Urville Antartic station (60°40'S; 40°01'E), the same place as the instantly disclosed bacterium. Hoyoux et al. further teach the characterization of this β-galactosidase and teach that the β-galactosidase is active at 4°C in milk (in the presence of Ca). Hoyoux et al. further assayed the enzyme activity at various temperatures from 5°C to 60°C and

showed that after 50°C the enzyme became inactivated and the enzyme had a broad pH stability, ranging from 6.5 to 10.

Thus the DNA of Francois et al., in light of the evidence presented by Hoyoux et al., anticipates those claims to a purified cold-active β-galactosidase specific for lactose having a stable enzymatic activity below 8°C (claims 3 and 4) and wherein said β-galactosidase is produced by a strain of a psychrophilic bacterium, *Pseudpaltermonas haloplanktis* (claim 5).

Claims 3, 4, 9, 10, 11, 13, 15, 17, 19, 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Trimbur et al. (Applied and Enviromental Microbiology, Vol. 60, No. 12, pp 4544-4552, December 1994, See IDS).

Trimbur et al. teach the isolation and cloning of the gene which encodes a cold-active β-galactosidase specific for lactose from the psychrotrophic microorganism, *Arthrobacter*. Trimbur et al. further teach the purification of this enzyme from *E. coli* in which it was recombinantly expressed. Trimbur et al. teach the effect of a number of ions on the β-galactosidase activity including 1mM $CaCl_2$, in which the enzyme retained 61 % of its activity. Trimbur et al. teach the effect of temperature on the enzyme activity by assaying at increments between 4 and 60°C. Trimbur et al. teach that the enzyme has a pH optimum of 7.2. Maximum activity was found at about 40°C and the enzyme retained approximately 25% of its activity at 10°C and incubation at 50°C caused inactivation within 10 minutes. While it is admitted that Trimbur et al. do not actually report the activity of the taught β-galactosidase at a temperature below 8°C, they do

report that the enzyme retained approximately 25% of its activity at 10°C, just 2° greater than 8°C. This in combination with applicants own definition of "stable enzymatic activity" on page 4, lines 9-12 of the specification, which states that "an enzymatic activity is considered as stable when, in the concerned conditions, the enzyme is capable of lasting long enough to obtain the desired effect, for example, the hydrolysis of a substrate." leads the examiner to believe that the enzyme of Trimbur et al. has "stable enzymatic activity" at a temperature below 8°C, and thus anticipates this limitation.

Trimbur et al. further teach this DNA in a recombinant plasmid with expression control sequences and in a transformed bacterial cell.

Thus the teachings of Trimbur et al. anticipate a claim to a purified cold-active β-galactosidase specific for lactose having a stable enzymatic activity below 8°C.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
12/14/2006